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PATENT- OG VAREMÆRKESTYREL

A sensor

Field of the invention

The present invention relates to a sensor comprising one or more sensor units, wherein each sensor units comprises a surface stress sensing element and wires connected to the surface stress sensing element for applying a voltage over the surface stress sensing element. One type - the most commonly used type of sensor unit - is a cantilever.

Background of the invention

In the prior art, such cantilevers have been used in atomic force microscopy technology (AFM) and in the art of detecting components in fluids such as gas and liquids.

It is known from e.g. WO 0066266 and WO 9938007 that micro cantilevers can be used for detection of molecular interaction. Capture molecules are immobilised on the surface of the cantilever. The capture molecule can basically be any molecule that specifically binds to another molecule. Capture molecules can be DNA oligoes, proteins, antigen, antibodies, ligands, etc. When the capture molecules bind to an analyte in the sample that is presented to the cantilever, this will induce a change in the surface stress of the cantilever, and consequently the cantilever will deflect.

By measuring the reflection angle of a laser beam that is directed to the cantilever the deflection can be detected. This principle is also known from the atomic force microscopy (AFM). Another detection principle is the use of a piezoresistor integrated into the cantilever for detecting the surface stress directly. In this detection principle the deflection is detected as a change in the electrical resistance of the piezoresistor.

For stress formation studies in ambient and aqueous environments, micrometer-sized cantilevers with optical read-out have proven very sensitive as described in the articles Berger, R., Gerber, Ch., Lang, H.P. & Gimzewski, J.K. Micromechanics: A toolbox for femtoscale science: "Towards a laboratory on a tip". *Microelectronic Engineering.* **35**, 373-379 (1997), and O'Shea, S.J., Welland, M.E. Atomic force Microscopy stress sensors for studies in liquids. *J. Vac. Sci. Technol. B.* **14**, 1383-1385 (1996).

Basically, a biochemical reaction at the cantilever surface can be monitored as a bending of the cantilever due to a change in the surface stress. Surface stress changes in self-assembled alkanethiols on gold have earlier been measured in air by this technique, and surface stress changes of approximately 10^{-5} N/m can be resolved by cantilever-based methods. This sensor principle has a wide range of applications in the detection of specific biomolecules as well as in real time local monitoring of chemical and biological interactions.

Cantilever-based sensors with integrated piezoresistive read-out are described by Thaysen, J., Boisen, A., Hansen, O. & Bouwstra, S. AFM probe with piezoresistive read-out and highly symmetrical Whetstone bridge arrangement. *Proceedings of Transducers'99*, 1852-1855 (Sendai 1999). Hereby the stress changes on the cantilever sensors can be registered directly by the piezoresistor. Moreover, integrated read-out greatly facilitates operation in solutions since the refractive indices of the liquids do not influence the detection. Each sensor has a built-in reference cantilever, which makes it possible to subtract background drift directly in the measurement. The two cantilevers are connected in a Whetstone bridge, and the stress change on the measurement cantilever is detected as the output voltage from the Whetstone bridge.

In the prior art realisations of cantilever-based sensors with piezoresistive read-out, the piezoresistors are contacted through 'horizontal' wiring on the sensor chip, i.e. the electrical wires are placed parallel to the surface of the cantilever arm and the surface of the substrate carrying the cantilever. Figure 1 shows such prior art cantilever. The wiring takes up a considerable amount of space and is therefore a crucial limiting factor when trying to maximise the number of cantilevers on a sensor chip. Furthermore, the horizontal wiring makes it very difficult to build two dimensional arrays of cantilever sensors. As described in WO 0066266, it is feasible to place two rows of cantilever sensors facing each other, but if additional rows of cantilevers are added the spacing between adjacent rows will increase significantly due to the electrical wiring. Moreover, it is not possible to place more than two rows of

cantilevers in a liquid handling system. That is, cantilevers on either side of a liquid channel.

Summary of the invention

The objective of the present invention is to provide a sensor suitable for use in the detection of one or more components in a fluid, which the disadvantages discussed above disadvantages.

In particular, one objective of the invention to provide a sensor which can be incorporated into or constitute a microchip and wherein two or more sensor units comprising wires for applying a voltage can be incorporated, thereby overcoming the wiring problem discussed above.

A further objective of the present invention is to provide a sensor of micrometer dimensions comprising one or more sensor units, which allows freedom of design with respect to the sensor and freedom of positioning with respect to the sensor units.

Yet a further objective of the present invention is to provide a sensor of micrometer dimensions where the number of sensor units may be increased without reducing the sensitivity of the sensor.

These and other objectives have been achieved by the invention as defined in the claims.

Disclosure of the invention

The sensor according to the invention comprises a primary substrate and at least one sensor unit connected to the primary substrate. Normally the primary substrate and the sensor unit will be made in one piece, e.g. using photo resist technology as it is generally known. But the sensor unit and the primary substrate may be prepared separately and thereafter connected to each other, e.g. using welding techniques, glue or other well-known techniques.

The sensor unit comprises a surface stress sensing element. Such surface stress sensing element is generally known in the art and includes in particular a surface stress sensing element that acts by applying a voltage over the stress sensing element, where after the surface stress can be measured as a change in resistance, a change in capacity or other changes of electric signal. Alternatively the surface stress, in the form of a deflection or in the form of a change in resonance frequency in case the sensor unit is amplified, may be measured using laser technology as known from the prior art technology, e.g. as described in WO 0058729, US 6016686 and US 6289717 which are hereby incorporated by reference. It is preferred that the surface stress sensing element is a capacitor and/or a piezoresistor and/or a piezo electric unit. The capacitor may be in the form of two conducting elements of e.g. metal or conductive polymers separated a short distance e.g. between 0.5 and 3 µm from each other by a non-conductive material such as liquid, gas or solids e.g. air, dielectricum, and octafunctional epoxidized novalac e.g. SU-8. The piezo electric unit e.g. of a material selected from the group consisting of quartz, PZT, PVDF, ZnO or solgel. The piezoresistor may e.g. be of a material

selected from the group consisting of amorph polysilicon (single crystal Si), metal or metal containing composition e.g. gold, AlN, Ag, Cu, Pt and Al, conducting polymers such as, doped octafunctional epoxidized novalac e.g. doped SU-8. In particular, it is preferred that the surface stress sensing element is a piezoresistor. Such piezoresistor is well known in the art and is e.g. described in the following publications which are hereby incorporated by reference: US 6237399, US 5907095, Berger, R. et al. Surface stress in the self-assembly of alkanethiols on gold. *Science*. **276**, 2021-2024 (1997); Berger, R., Gerber, Ch., Lang, H.P. & Gimzewski, J.K. Micromechanics: A toolbox for femtoscale science: "Towards a laboratory on a tip". *Microelectronic Engineering*. **35**, 373-379 (1997); Thaysen, J., Boisen, A., Hansen, O. & Bouwstra, S. AFM probe with piezoresistive read-out and highly symmetrical Whetstone bridge arrangement. *Proceedings of Transducers'99*, 1852-1855 (Sendai 1999); Boisen A., Thaysen J., Jensenius H., & Hansen, O. Environmental sensors based on micromachined cantilevers with integrated read-out. *Ultramicroscopy*, **82**, 11-16 (2000).

The primary substrate in connection with the sensor unit may in principle have any shape generally known in the art.

The primary substrate may in principle be of any type of material, such as one or more of the materials selected from the group consisting of silicon, silicon nitride, silicon oxide, metal, metal oxide, glass and polymer, wherein the group of polymers preferably includes epoxy resin, polystyrene, polyethylene, polyvinylacetate, polyvinylcloride, polyvinylpyrrolidone,

polyacrylonitrile, polymethylmetacrylate, polytetrafluoroethylene, polycarbonate, poly-4-methylpentylene, polyester, polypropylene, cellulose, nitrocellulose, starch, polysaccarides, natural rubber, bytyl rubber, styrene butadiene rubber and silicon rubber.

In order to have optimal processability, the primary substrate should preferably be of or comprise a material which can act as a photo resistor. Preferred materials include an epoxy resin, preferably selected from the group consisting of epoxy functional resin having at least two epoxy groups, preferably an octafunctional epoxidized novalac. Particularly preferred materials are described in US 4882245 which is hereby incorporated by reference. The most preferred material is the octafunctional epoxidized novalac which is commercially available from Celanese Resins, Shell Chemical, MicroChem Inc under the tradename SU-8, and from Softec Microsystems under the tradename SM10#0.

Basically, it is preferred that the sensor unit is based on a material included in the primary substrate or preferably on the same material as that of the primary substrate. If the sensor unit and the primary substrate are made in one piece, it is naturally based on the same material, but the sensor unit and the primary substrate may include one or more layers of material not included in the other part.

If the sensor unit and the primary substrate are made in separate pieces and connected afterwards, the material should at least be compatible with each other, and

preferably the major weight part of the materials should be identical.

For applications in liquid, the wires need to be insulated, and the primary substrate should therefore preferably consist of or comprise an electrically insulating material, which prevent short-circuiting of the electrical connections during operation. The insulating material could e.g. be a polymer, silicon nitride, silicon oxide, metal oxides, etc. In case the electrical connection line includes doped silicon, the insulating property can be obtained by reversed biased diode effect. For a wire consisting of p-type silicon, the reversed biased diode effect is obtained by encapsulating the wire in n-type silicon.

The sensor according to the invention includes an electric communication line for applying a voltage over the surface stress sensing element. The electric communication line includes a pair of wires connected to the surface stress sensing element. The electric wire may be of the same material as the surface stress sensing element, particular if the surface stress sensing element is a piezoresistor. In this situation where the surface stress sensing element and the piezoresistor are of the same material the piezoresistor will preferably be of thinner e.g. a thinner layer or a thinner wire diameter. In other situation the surface stress sensing element and the piezoresistoris of different materials, and are fixated to each other in a connection point e.g. by welding. The method of connecting wires to a surface stress sensing element is generally known in the art, and reference is made to the prior art referred to above. The

electric communication line may consist of the wires, but it may also include other elements such as diodes, other resistors, e.g. a part of a Whetstone bridge or other surface stress sensing elements of the sensor.

At least one of the wires of the pair of wires is integrated in the primary substrate. If several wires are integrated in the primary substrate, the wires should be separated by insulating material for preventing short circuiting.

A high degree of design freedom may e.g. be achieved by integrating the wire(s) in the primary substrate so that they do not follow any surface which is substantially parallel +- 10° to a major surface of the sensor unit in a non-stressed state.

In the following any positions of the sensor unit or the surface stress sensing element refer to the sensor unit/ surface stress sensing element in non-stressed state.

A further high degree of design freedom may e.g. be achieved by integrating at least two wires in the primary substrate so that at least two wires pass in a direction different from each other through the material of the primary substrate.

It is preferred that other optional elements of electric communication line are not integrated in the primary substrate, but in some embodiments it may be convenient to at least partly integrate one or more of other elements of the electric communication line into the

primary substrate. This may e.g. reduce the size of the sensor.

The term "integrated in the primary substrate" as used herein means that the wire is embedded in the primary substrate material for at least a length of the wire, such as a length corresponding to at least half, preferably to the whole of the average thickness of the primary substrate, where the average thickness of the primary substrate is defined below.

The wire may e.g. be integrated in the primary substrate by passing through a channel in the primary substrate.

The sensor unit may in principle be any type of flexible unit which is usable in connection with surface stress sensing elements. Generally, it is preferred that the sensor unit is a flexible sheet-formed unit having an average thickness thinner than both its average thickness and its average width. Such sensor units preferably include cantilevers, bridges and diaphragms. In principle, however, the sensor unit may also be shaped a cord.

The thickness of the sensor unit may preferably be between 0.1 and 25 µm, more preferably between 0.3 and 5 µm, such as about 1 µm. The other dimensional parameters, thickness, width and or diameter, may preferably be up to about 500 µm, more preferably up to about 100 µm, such as about 50 µm.

In one embodiment, the sensor unit is a flexible sheet-formed unit with an average thickness of at least 5 times, preferably at least 50 times less than its average

width, and/or the sensor unit is a flexible sheet-formed unit having an average thickness of at least 5 times, preferably at least 50 times less than its average length. As the sensor unit may have shapes with no unambiguous definition of width and length, e.g. rounded or circular shapes, it is generally preferred that such a sensor unit is in the form of a sheet-formed unit with an average thickness of at least 5 times, preferably at least 5 times less than its other dimensions including width, length and diameter. In case the sensor unit is of rounded or circular shapes the following referenced to respectively, width and length, means respectively the shortest and the longest diameter or stub diameter.

The term "flexible" used in relating to the sensor unit, means that the sensor unit should be capable of deflect due to the stress formed in the surface stress sensing element using a voltage in the range which can be withstand by the surface stress sensing element e.g. a voltage up to about 1000 V, such as up to 300 V, or 220 V.

The connection line between the sensor unit and the primary substrate may be identified according to its material thickness i.e. the primary substrate is more rigid than the sensor unit, e.g. more than 3, 5 or 10 times as rigid as the sensor unit. The primary substrate may e.g. be thicker than the sensor unit, e.g. more than 3, 5 or 10 times or even more as thick as the sensor unit. The connection line between the sensor unit and the primary substrate is in the following denoted the stem of the sensor unit, and the tangent plane to the stem on the upper surface side of the sensor unit is measured on the sensor unit side of the stem. In situations where the

sensor unit has a plane upper surface, the tangent plane is identical to the plane defined by the surface. In situations where the connection line between the sensor unit and the primary substrate is not straight, e.g. a rounded stem, there may be several tangent planes to the stem. The tangent plane or planes to the stem of the upper surface of the sensor unit is in the following called the sensor unit plane or planes

The sensor unit of the sensor according to the invention may be in the form of a sheet-formed unit with two major surfaces defined as the upper surface and the lower surface, respectively.

The uppermost surface of said primary substrate can be identified as the surface of the primary substrate having an angle closest to 180° to one of the major surfaces of the sensor unit. In some situation the primary substrate may have more than one uppermost surfaces, and in this situation the condition stated herein with relation to the uppermost substrate should mean one of the uppermost substrate surfaces, preferably 2 or even all uppermost surfaces.

The upper surface of the sensor unit can be identified as the one of two major surfaces closest to the uppermost surface of the primary substrate. Thus a sensor in some situations may have two upper surfaces, and in this situation the condition stated herein with relation to the upper surface of the sensor unit should mean one of the upper surface of the sensor unit, both of the upper surfaces of the sensor unit.

The sensor unit is connected to the primary substrate so that it protrudes from the primary substrate. In this embodiment it is preferred that the upper surface or the sensor unit plane or planes has an angle to the uppermost surface of the primary substrate between 135° and 225°, preferably between 150° and 210°, such as between 165° and 195°. It is even more preferred that the upper surface of the sensor unit is substantially parallel to the uppermost surface of the primary substrate. In this connection it should be observed that "substantially parallel" includes a deviation of up to 10°, preferably up to 5°. Also, it should be observed that the uppermost surface of the primary substrate and the upper surface of the sensor unit preferably are in direct prolongation of each other. This embodiment is generally more simple to produce using standard photo-resist technique.

In situations where the wires and the surface stress sensing element has a connection point ass described above, the uppermost surface of the primary substrate may be identified as the primary substrate surface closest to the point of connection between the wire and the surface stress sensing element.

The lowermost surface of the primary substrate is defined as the surface opposite the uppermost surface, the lowermost surface is preferably substantially +- 10° parallel with the uppermost surface. The average thickness also called the thickness of the substrate is defined as the average distance between the uppermost surface and the lowermost surface measured perpendicular to the uppermost surface.

It is preferred that the wire or other parts of the electric communication line pass through the primary substrate material and exit the primary substrate to provide an electric communication line exit. The distance between the wire and the uppermost surface may preferably differ from the point of connection between the wire and the surface stress sensing element, or from the stem of the surface stress sensing element to the electric communication line exit.

For optimising the design freedom the wire may preferably be integrated into said primary substrate so that the distance between the wire and the uppermost substrate surface differs along the wire e.g. at least a part of the length of the wire, so that preferably at least 10 % of the wire has a distance which is different from another distance between the uppermost substrate surface and the wire. This means in practice that the wire passes through the material and may exit the material at any desired point, and thereby the design freedom is highly increased. The distance between the wire and the uppermost primary substrate surface may e.g. differ along at least 50 %, such as at least 75 % or even more preferably all of the length of the integrated wire.

In a preferred embodiment the wire or wires exit the primary substrate at its lowermost surface.

The uppermost surface of the primary substrate may preferably be substantially plane, where "substantially plane" should be interpreted as macroscopic plane surface, wherein the surface preferably is free of irregular cavities. It is particularly preferred that the wire passes through the primary substrate in a sum line

of at least 10°, such as at least 45° or at least 65°, to the uppermost surface substrate. It should be observed that "sum line" means the straight line either between the point of connection between the point of connection between the wire and the surface stress sensing element, or the stem of the surface stress sensing element and the electric communication line exit.

It is even more preferred that the wire passes through the primary substrate in a sum line of about 90° to the uppermost surface primary substrate. By having an angle that is close to perpendicular to the uppermost surface of the primary substrate, the wire may pass through the primary substrate and exit at the lowermost surface of the primary substrate, which makes it possible to increase the number of sensor units.

It is particularly preferred that both of the wires of said electric communication line pass through the primary substrate material in a straight line and exit the primary substrate through the lowermost surface, e.g. at an angle between the wire and the uppermost substrate surface which is about 90° +- 10° in order thereby to provide electric communication line exits at the lowermost substrate surface. A wire having this angle to the uppermost substrate surface will in the following also be denoted as a vertical wire.

It is preferred that the wire is at least in 50 % of its primary substrate integrated length is perpendicular +- 10°, preferably +- 10°, to sensor unit plane or planes.

In one embodiment, both of the wires of the electric communication line pass through the primary substrate material in a substantially straight line, wherein "substantially straight" includes a partial deviation from the sum line of up to 10 %, preferably up to 5 % of the length of the sum line. The wires may preferably be vertical.

It is particularly preferred that the sensor unit is a cantilever, preferably a cantilever in the form of a sheet-formed unit having a thickness which is thinner than its other dimensions. The cantilever is connected to the primary substrate and protrudes therefrom in one or more cantilever protruding directions.

The cantilever may preferably have a plane upper surface, and preferably also a plane lower surface when in a non-stressed state. It should, however, be observed that the cantilever may be curved or bended even in a non-stressed state.

In a preferred embodiment, the cantilever has a plane, non-curved upper surface in a non-stressed state. The upper surface of the cantilever is one of two major surfaces, where the upper surface is closest to the uppermost surface of the primary substrate measured at the stem of the cantilever.

It is preferred that the uppermost surface of the primary substrate is substantially parallel +- 10° with said the cantilever upper surface.

The cantilever protrudes from the primary substrate in one or more cantilever protruding directions to provide a

free edge of the cantilever. The two-dimensional cantilever shape defined as the shape surrounded by the cantilever free edge and the stem line along the connection to the primary substrate may preferably be selected from the group consisting of square, rectangular, triangular, pentagonal, hexagonal, leaf shaped, circular and oval periphery.

In a particularly preferred embodiment of the sensor according to the invention where the sensor unit includes a cantilever, both of said wires in the pair of wires pass vertically through the primary substrate, such as in a sum angle which is substantially (+- 10°) perpendicular to the substrate surface. The primary substrate is preferably shaped as a pillar, wherein the centre line of the pillar preferably is perpendicular +- 20° to said uppermost surface of said primary substrate. The wires preferably pass through the primary substrate and exit the pillar at its lowermost surface.

The pillar may preferably be connected to a secondary substrate comprising a circuit for applying the voltage, said secondary substrate preferably being an electronic chip comprising contact pads corresponding with said wire exits.

Each pillar may comprise two or more cantilevers, wherein the wires of said cantilevers preferably pass vertically through the material of the pillar, and where the cantilevers protrude from the pillar. In this embodiment, it is preferred that the cantilevers have two-dimensional cantilever shapes which are substantially identical to each other, more preferably the two-dimensional cantilever shapes are preferably selected from the group

consisting of square, rectangular, triangular, pentagonal, hexagonal and leaf shaped.

Such pillar or pillars comprising one or more cantilevers will in the following also be denoted "free hanging cantilever element".

In an alternative embodiment, the sensor unit is a bridge, preferably in the form of a sheet-formed unit having a thickness which is thinner than its other dimensions, length and width, which bridge is connected to and stem from said primary substrate to link two primary sub substrate sections in a bridge.

The bridge may preferably have a plane upper surface and preferably also a plane lower surface when the bridge is in a non-stressed state. It should, however, be observed that the bridge may be curved or bended even in a non-stressed state.

In a preferred embodiment, the bridge has a plane, non-curved upper surface in a non-stressed state. The upper surface of the bridge is one of two major surfaces, where the upper surface is closest to the uppermost surface of the primary sub substrate section or sections wherein the wire(s) is/are integrated at the stem of the bridge to the primary sub substrate section or sections. It should be noted that in extreme situations both surfaces of the bridge may constitute upper surfaces. In this situation it is preferred that at least one of the upper surfaces is plane.

The bridge may preferably have a plane surface in a non-stressed state. In one embodiment, each primary sub

substrate section has an uppermost surface defined as the primary sub substrate surface closest to the point of connection between the respective wire and the surface stress sensing element. The uppermost substrate surface may preferably be substantially parallel(+- 10°) with the upper surface of the bridge.

Both of said wires in the pair of wires may preferably pass through one of the primary sub substrate sections in a sum line which is substantially (+- 10°) perpendicular to the primary sub substrate section through which it passes. One or both of said primary sub substrate sections may preferably be shaped as pillars. The centre line of the pillars may e.g. be perpendicular +- 20° to said uppermost surface of the respective primary sub substrate section. Thereby the wires pass through the substrate and exit the pillar or pillars at its lowermost surface and an improved design freedom is obtained.

As for the cantilever containing pillars, the pillar may be connected to a secondary substrate as described above. The pillars may comprises two or more bridges, the wires of said bridges passing through the material of the pillars, and said bridges being connecting to two or more pillars.

Such pillar or pillars comprising one or more bridges will in the following also be denoted "free hanging bridge element".

In yet another alternative, the sensor unit is a diaphragm, preferably in the form of a sheet-formed unit having a thickness which is thinner than its other dimensions, length, width and/or diameter. The diaphragm

is connected to and stem from the primary substrate and protrudes therefrom.

The diaphragm may preferably have a plane, non-curved upper surface in a non-stressed state. It should, however, be observed that the diaphragm may be curved or bended even in a non-stressed state.

The upper surface of the diaphragm is one of two major surfaces, where the upper surface closest to the upper surface of the primary substrate at the stem of the diaphragm. The uppermost surface of the diaphragm may e.g. be parallel +- 10° with the uppermost surface of the primary substrate.

In a preferred embodiment, the diaphragm has a plane, non-curved upper surface in a non-stressed state.

Both of the wires in the pair of wires may preferably pass through the primary substrate in a vertical sum line which is substantially (+- 10°) perpendicular to the upper substrate surface. The primary substrate may preferably be shaped as a pillar with an open centre covered by the diaphragm, and the centre line of the pillar may preferably be perpendicular +- 20° to the uppermost surface of the primary substrate

As described above for the sensor with cantilever sensor unit, the pillar may be connected to a secondary substrate.

Such pillar or pillars comprising one or more diaphragms will in the following also be denoted "free hanging diaphragm element". The general term for pillars

comprising one or more sensor units as defined above is "free hanging sensor unit element".

Using the free hanging sensor unit element comprising pillar structures makes it possible to realise high-density two dimensional arrays. The sensor units in the array can be placed with the same spacing as used in DNA chips, e.g. as described in US 6254827, and an array of sensor units can straightforwardly be used in the same type of applications as in the DNA chip. The signal from DNA chips is today read-out by the use of rather bulky optical detector systems and fluorescently labelled molecules. The present invention makes it possible to realise an array with the same performance but with a simple electrical and label free detection scheme. The sensor units may e.g. be functionalised with the same array sputter techniques as used in DNA chip production. Any other method may be used, e.g. as described in WO 0066266, WO 9938007, US 5,156,810, WO 0036419 and WO 9631557, which publications are hereby incorporated by reference.

The free hanging sensor unit may also be placed in an interaction chamber, such as e.g. a flow channel. This can e.g. be used in micro liquid handling systems. The sensor therefore may comprise a fluid channel where the sensor units protrude into the fluid channel as disclosed in e.g. WO 9938007 and WO 0066266.

As also described in WO 0066266, the fluid channel may include an interaction chamber, and the sensor units e.g. in the form of free hanging sensor unit element may

preferably be integrated into the wall of said interaction chamber.

In one embodiment, an electrode can also be placed on the free hanging sensor element and electrically connected through the pillar. By controlling the potential of the electrodes, this can e.g. be used for immobilization of charged molecules or for direction of molecules since the electrode can form an electro endo-osmotic liquid flow towards the sensor.

The sensor according to the invention may in general include a secondary substrate supporting said primary substrate or primary sub substrate sections, e.g. in the form of free hanging sensor unit elements. The secondary substrate may comprise an electric communication line for applying a voltage over the respective pair of wire(s). The wires may e.g. be guided through the secondary substrate.

The secondary substrate may be an electronic chip comprising contact pads corresponding with said wire exits.

In a preferred embodiment, the sensor comprises a secondary substrate comprising an array of sensor units connected to the primary substrates, preferably in the form of free hanging sensor unit element, wherein the wires are incorporated in the primary substrate material.

The sensor may be in the form of a microchip, which means that none of its dimensions should exceed 10000 µm, preferably none of its dimensions should exceed 5000 µm.

The sensor according to the invention may preferably comprise at least one sensor unit having a target surface area, which area has been functionalised by linking, preferably by covalently linking of one or more functional groups comprising a detection ligand to said target surface area, said detection ligand being a member of a specific binding pair. Further information relating to this aspect can be found in WO 0066266 and DK patent application PA 200101724 which are hereby incorporated by reference. From these publications information relating to reference units can also be found.

It is thus preferred that the sensor comprises at least two sensor units, at least one of said sensor units being a reference units. The reference unit may preferably comprise a target surface area, which area has a surface chemistry which is different from the sensor unit for which the reference unit acts as reference, preferably said target surface area has been functionalised by linking, preferably by covalently linking of one or more functional groups, wherein said one or more functional groups linked to the surface area of said reference unit or its concentration are different from the sensor unit for which the reference unit acts as reference.

The sensor according to the invention may preferably be used for detection of substances in gasses or liquids, preferably in liquids wherein the substances include biomolecules such as RNA oligos, DNA oligos, PNA oligos, protein, peptides, hormones, blood components, antigen and antibodies.

The wire or wires may be integrated in the primary substrate using any technology, e.g. by casting or

moulding the material of the primary substrate around the wire(s). The wire(s) may e.g. be layered between primary substrate material layers, which layers may be of similar or different materials. In a preferred embodiment, the primary substrate is prepared by e.g. using photo-resist technology as referred to above. The primary substrate may be prepared with a channel, or this channel may be provided afterwards. The channel should be applied through the primary substrate in a line as described for the wire above. Thereafter the channel is filled with a conducting material e.g. a metal e.g. by using electroplating.

The sensor could be bonded to external electrical circuits using flip-chip technology, e.g. as described in US 6254827 which is hereby incorporated by reference. The primary substrates in the form of pillars can be fabricated directly on an electronics chip.

Brief description of drawings

Figure 1 is a cross-sectional view of a prior art cantilever sensor.

Figures 2a-2c are cross-sectional views of 3 different cantilever sensors according to the invention.

Figure 3 is a top view of a free hanging cantilever element according to the invention.

Figure 4 is a cross-sectional view of a free hanging cantilever element placed on a secondary substrate.

Figures 5-7 are top views of different embodiments of free hanging cantilever element according to the invention.

Figure 8 is a cross-sectional view of a free hanging bridge element placed on a secondary substrate.

Figure 9 is a top view of a free hanging cantilever element according to the invention wherein the cantilever comprises 4 individual cantilevers.

Detailed description of drawings

Prior art cantilever sensors for detecting of substances e.g. as disclosed in WO 9938007, generally have shapes as shown in figure 1. The shown prior art cantilever sensor comprises a primary substrate 1 and a cantilever unit 4 connected to the primary substrate 1. A surface stress sensing element 3 e.g. a piezoresistor such as a horseshoe-shaped piezoresistor is placed on the surface of the cantilever unit 4, and a pair of parallel wires 2 are placed on the uppermost surface 5 of the primary substrate 1.

Figures 2a-2c shows cross-sectional views of three different cantilever sensors according to the invention. The cantilever sensors comprise respectively a primary substrate 21a, 21b, 21c, and a cantilever sensor 24a, 24b, 24c. In the cantilever sensor shown in figure 2a, a surface stress sensing element 23a e.g. a piezoresistor such as a horseshoe-shaped piezoresistor is incorporated

into the cantilever unit 24a, and a pair of parallel wires 22a are integrated into the primary substrate as vertical wires i.e. the wires 22a have an angle to the uppermost substrate 25a which is about 90°, and they pass through the primary substrate and exit a its lowermost surface 27a. As indicated in the figure the surface stress sensing element 23a and the wires 22a is of a different material and comprises a connection point 26a. The uppermost surface of the primary substrate 22a and the upper surface of the cantilever unit 28a are parallel, and are in direct prolongation of each other.

In the cantilever sensor shown in figure 2b, a surface stress sensing element 23b e.g. a piezoresistor such as a horseshoe-shaped piezoresistor is placed at the surface of the cantilever unit 24b, and a pair of parallel wires 22b are integrated into the primary substrate. The wires pass through the primary substrate in a straight line and with an angle to the uppermost substrate 25b which is about 45°. As in the sensor of figure 2a, the surface stress sensing element 23b and the wires 22b is of a different material and comprises a connection point 26b. The uppermost surface of the primary substrate 22b and the upper surface of the surface stress sensing element 28b are parallel and are in direct prolongation of each other.

The cantilever sensor shown in figure 2c, is a combination of the cantilevers of figures 2a and 2b, wherein surface stress sensing element 23c is placed at the surface of the cantilever unit 24c, and a pair of

parallel wires 22c are integrated into the primary substrate 21a as vertical wires. In figure 2c, the connection line between the primary substrate 21a and the cantilever unit 24c also denoted the stem of the cantilever unit, is indicated with the line 29c.

Figure 3 shows a top view of a free hanging cantilever element according to the invention. The cantilever unit 31 is ring shaped, and protrude from the pillar 32 to which it is connected. The surface stress sensing element 33 in the form of a piezoresistor is placed in a circle on the surface of the cantilever unit 31. It should be observed that it is generally preferred that the surface stress sensing element is embedded in the material of the sensor unit to thereby minimise undesired environmental interference. The surface stress sensing element passes to the stem 34 of the cantilever unit and the wires 35 passes vertical through the pillars. As indicated the piezoresistor 33 and the wires 35 are of identical materials.

Figure 4 is a cross-sectional view of a free hanging cantilever element placed on a secondary substrate 45 e.g. a chip substrate. The free hanging cantilever element comprises a pillar 41 (primary substrate) and two individual cantilever units 42. Each of the cantilever units 42 comprises a piezoresistor 43 embedded in the cantilever sensor material. The piezoresistors are connected to wires 46, which may be of same material, and the wires pass vertical through the pillar 41 and exit at the lower surface of the pillar 41, into the material of the secondary substrate 45.

The free hanging cantilever element shown in figure 5 is similar to the free hanging cantilever element shown in figure 3 except that the piezoresistor 53 is placed in a different pattern on the cantilever unit 51. The stem of the cantilever 53 has not been marked in figure 5.

The free hanging flower-shaped cantilever element shown in figure 6 is similar to the free hanging cantilever element shown in figures 3 and 5 except that the piezoresistor 63 is placed in a different pattern on the cantilever unit 61. The stem of the cantilever 63 has not been marked in figure 6.

In a not shown variation of the flower-shaped sensor according to the invention shown in figure 6, each leaf of the flower is an individual cantilever unit comprising a piezoresistive element.

The free hanging cantilever element shown in figure 7 is another version similar to the free hanging cantilever element shown in figures 3, 5 and 6. This free hanging cantilever element differs in that four cantilever cantilever units 71 are connected to the pillar 72 and protrudes from the pillar 72. The cantilever units 71 are partly connected to each other and consequently the stress formation on one of the cantilever unit mat influence the measurement on another one of the sensor units. Each of the cantilever units 71 comprises a piezoresistor 73. The piezoresistor passes to the stem 74 of the respective cantilever unit 71, and the wires 75 passes vertical through the pillars.

Figure 8 is a cross-sectional view of a free hanging bridge element placed on a secondary substrate e.g. a chip substrate. The free hanging bridge element comprises two pillars 81 (primary sub substrate) and a bridge sensor unit 82 connected to the two pillars 81. The bridge unit comprises a piezoresistor 83 embedded in the bridge sensor material. The piezoresistor are connected to two wires, which may be of same material as the piezoresistor, and the wires pass vertical through the pillars 81 and exit at the lower surfaces of the pillar 81, into the material of the secondary substrate 85.

Figure 9 is a top view of a free hanging cantilever element with 4 individual cantilever units 92 connected to the pillar 91. The cantilever units comprises not shown surface stress sensing element incorporated to the material of the cantilever units 92, and the pillar 91 comprises not shown vertical wires.

Example

An example of the fabrication of a high-density 2-dimensional array of cantilever-based sensors placed on stand-alone pillars is described briefly below.

The circuits connecting for connecting individual pillars is defined on a secondary substrate in the form of a separate chip using standard microelectronics techniques. Next, the electronics chip is coated by an insulating film, for example the polymer SU8. Windows are opened in the SU8 above the electrical contact pads on the

electronics chip. A second layer of SU8 is spin coated on the chip and pillars centred on the contact pads are defined. One or more vertical channels are running inside the pillars, thereby creating contact to the electronics chip below. These channels are then filled with a metal by for example electroplating. After that, a photoresist is spun on the structures and planarized so that the resist has about the same height as the pillars. Windows are opened in the resist to the electroplated wires. The resist is hard baked. The bottom of the cantilevers is defined in SU8 and the piezoresistores connected to the electroplated vertical wires are defined in gold. Finally, the top part of the cantilevers is defined in SU8, hereby completely encapsulating the resistors. The planarized resist is dissolved resulting in free hanging cantilever structures.

Patent Claims:

1. A sensor comprising a primary substrate and a sensor unit connected to said primary substrate, said sensor unit comprising at least one surface stress sensing element preferably selected from the group consisting of a piezo electric element a capacitor and a piezoresistor, and an electric communication line for applying a voltage over said surface stress sensing element, said electric communication line including a pair of wires connected to said surface stress sensing element, at least one of said wires being integrated in said primary substrate, said wire preferably being integrated in said primary substrate by passing through a channel in said primary substrate.

2. A sensor according to claim 1 wherein said sensor unit is a flexible unit selected from the group consisting of a cantilever, a bridge and a diaphragm.

3. A sensor according to any one of the claims 1 and 2 wherein said sensor unit is a flexible sheet-formed unit having an average thickness which is thinner than both its average thickness and its average width.

4. A sensor according to any one of the claims 1, and 3 wherein said sensor unit is a flexible sheet-formed unit having an average thickness which is at least 5 times, preferably at least 50 times less than its average width.

5. A sensor according to any one of the claims 1-4 wherein said sensor unit is a flexible sheet-formed unit

having an average thickness which is at least 5 times, preferably at least 50 times less than its average length, said sensor unit preferably being a flexible sheet-formed unit having an average thickness which is at least 5 times, preferably at least 50 times less than its other dimensions.

6. A sensor according to any one of the claims 1-5 wherein said sensor unit is a flexible sheet-formed unit having two major surfaces, said sensor unit being connected to said primary substrate so that it protrudes from the primary substrate, said upper surface of said sensor unit having an angle to an uppermost surface of said primary substrate between 135° and 225°, said upper surface of said sensor unit preferably being substantially parallel to an uppermost surface of said primary substrate, said uppermost surface of said primary substrate and said upper surface of the sensor unit preferably being in direct prolongation of each other.

7. A sensor according to any one of the claims 1-6 wherein said primary substrate has an uppermost surface, said wire being integrated into said primary substrate so that the distance between the wire and the uppermost primary substrate surface differs along at least a part of the length of the wire so that preferably at least 10 % of the wire has a distance which is different from another distance between the uppermost primary substrate surface and the wire, more preferably so that the distance between the wire and the uppermost primary substrate surface differs along at least 50 %, such as at least 75 % or even more preferably all of the length of the wire.

8. A sensor according to any one of the claims 1-7 wherein said primary substrate has an uppermost surface, said wire being integrated into said primary substrate so that the wire or other parts of the electric communication line pass through the primary substrate material and exit the primary substrate to provide an electric communication line exit, the distance between the wire and the uppermost surface preferably differing from the connection line between the primary substrate and the sensor unit, and the surface stress sensing element to the point of the wire closest to the electric communication line exit.

9. A sensor according to any one of the claims 7 and 8 wherein said uppermost surface of the primary substrate is substantially plane and said wire passes through the primary substrate in a sum line having an angle of at least 10°, such as at least 45° or at least 65° to the uppermost surface or the primary substrate.

10. A sensor according to claim 9 wherein said wire passes through the primary substrate in a sum line of about 90° to the uppermost surface primary substrate.

11. A sensor according to any one of the claims 1-10 wherein one or both of the wires of said electric communication line pass through the primary substrate material and exit the primary substrate to provide electric communication line exits.

12. A sensor according to any one of the claims 1-11 wherein one or both of the wires of said electric communication line pass through the primary substrate material in a substantially straight line.

13. A sensor according to any one of the claims 1-12 wherein said piezoresistor comprise or preferably consist of a material selected from the group consisting of amorph polysilicon (single crystal Si), metal or metal containing composition e.g. gold, AlN, Ag, Cu, Pt and Al, conducting polymers such as, doped octafunctional epoxidized novalac e.g. doped SU-8.

14. A sensor according to any one of the claims 1-12 wherein said capacitor in the form of two conducting elements of e.g. metal or conductive polymers seperated a distance of up to about 5 μm from each other by a non-conductive material selected from the group consisting of liquid, gas or solids e.g. air, dielectricum, and octafunctional epoxidized novalac e.g. SU-8.

15. A sensor according to any one of the claims 1-14 wherein said primary substrate comprises one or more of the materials selected from the group consisting of silicon, silicon nitride, silicon oxide, metal, metal oxide, glass and polymer, wherein the group of polymers preferably includes epoxy resin, polystyrene, polyethylene, polyvinylacetate, polyvinylcloride, polyvinylpyrrolidone, polyacrylonitrile, polymethylmetacrylate, polytetrafluoroethylene, polycarbonate, poly-4-methylpentylene, polyester, polypropylene, cellulose, nitrocellulose, starch, polysaccarides, natural rubber, bytyl rubber, styrene butadiene rubber and silicon rubber.

16. A sensor according to claim 14 wherein said primary substrate comprises an epoxy resin, preferably selected from the group consisting of epoxy functional

resin having at least two epoxy groups, preferably an octafunctional epoxidized novalac.

17. A sensor according to any one of the claims 1-16 wherein said sensor unit is based on a material included in the primary substrate, preferably said sensor unit is based on the same material as that of the primary substrate.

18. A sensor according to any one of the claims 1-17 wherein the sensor unit is a cantilever, said cantilever being a sheet-formed unit having a thickness which is thinner than its other dimensions, length and width, which cantilever is connected to and stem from said primary substrate and protrudes therefrom in one or more cantilever protruding directions.

19. A sensor according to claim 18 wherein said cantilever protrudes from the primary substrate in one or more cantilever protruding directions to provide a free edge of said cantilever, the two-dimensional cantilever shape being defined as the shape surrounded by the cantilever free edge and the stem line along the connection to the primary substrate, which shape preferably is selected from the group consisting of square, rectangular, triangular, pentagonal, hexagonal, leaf shaped, circular and oval periphery.

20. A sensor according to any one of the claims 18 and 19 wherein said primary substrate has an uppermost surface, said uppermost substrate surface being substantially parallel with the upper surface of the cantilever.

21. A sensor according to any one of the claims 18-20 wherein both of said wires in the pair of wires pass through the primary substrate in a sum angle which is substantially (+- 10°) perpendicular to the uppermost substrate surface, said primary substrate preferably being shaped as a pillar, the centre line of the pillar preferably being perpendicular +- 20° to uppermost surface, which wires pass through the primary substrate and exit the pillar at its lowermost surface.

22. A sensor according to claim 21 wherein said pillar is connected to a secondary substrate comprising a circuit for applying the voltage, said secondary substrate preferably being an electronic chip comprising contact pads corresponding with said wire exits.

23. A sensor according to any one of the claims 20-22 wherein said pillar comprises two or more cantilevers, the wires of which cantilevers pass through the material of the pillar, and which cantilevers protrude from the pillar, said cantilevers preferably having a two-dimensional cantilever shape which is substantially identical to each other, more preferably said two-dimensional cantilever shape preferably being selected from the group consisting of square, rectangular, triangular, pentagonal, hexagonal and leaf shaped.

24. A sensor according to any one of the claims 1-17 wherein the sensor unit is a bridge, said bridge being a sheet-formed unit having a thickness which is thinner than its other dimensions, length and width, which bridge is connected to and stem from said primary substrate to link two primary sub substrate sections in a bridge.

25. A sensor according to claim 24 wherein said primary sub substrate sections each has an uppermost surface, said bridge having an upper surface, which upper bridge surface being substantially parallel with the uppermost surface of said respective primary sub substrate section.

26. A sensor according to any one of the claims 24-25 wherein both of said wires in the pair of wires pass through one of the primary sub substrate sections in a sum angle which is substantially (+- 10°) perpendicular to the primary sub substrate section through which it passes, one or both of said primary sub substrate sections preferably being shaped as pillars, the centre line of the pillars preferably being perpendicular +- 20° to said uppermost surface of the respective primary sub substrate section, which wires pass through the substrate and exit the pillar or pillars at its lowermost surface.

27. A sensor according to claim 26 wherein said pillars are connected to a secondary substrate comprising a circuit for applying the voltage, said secondary substrate preferably being an electronic chip comprising contact pads corresponding with said exits of the wire.

28. A sensor according to any one of the claims 26-27 wherein said pillars comprise two or more bridges, the wires of which bridges pass through the material of the pillars, and said bridges being connecting with two or more pillars.

29. A sensor according to any one of the claims 1-17 wherein the sensor unit is a diaphragm, said diaphragm

being a sheet-formed unit having a thickness which is thinner than its other dimensions, length and width, which diaphragm is connected to and stem from said primary substrate and protrudes therefrom.

30. A sensor according to claim 29 wherein said primary substrate has an uppermost surface, said uppermost primary substrate surface being substantially parallel with the upper surface of said diaphragm.

31. A sensor according to any one of the claims 29-30 wherein both of said wires in the pair of wires pass through the primary substrate in a sum angle which is substantially (+- 10°) perpendicular to said uppermost surface, said primary substrate preferably being shaped as a pillar having an open centre covered by the diaphragm, the centre line of the pillar preferably being perpendicular +- 20° to the uppermost surface of the primary substrate, which wires pass through the primary substrate and exit the pillar at its lowermost surface.

32. A sensor according to claim 31 wherein said pillar is connected to a secondary substrate comprising a circuit for applying the voltage, said secondary substrate preferably being an electronic chip comprising contact pads corresponding with said exits of the wire.

33. A sensor according to any one of the preceding claims further comprising a secondary substrate supporting said primary substrate or primary sub substrate sections, said secondary substrate comprising an electric communication line for applying a voltage over the respective pair of wire or wires.

34. A sensor according to claim 33 wherein said wires are guided through the secondary substrate.

35. A sensor according to claim 33 wherein said secondary substrate is an electronic chip comprising contact pads corresponding with said exits of the wire.

36. A sensor according to any one of the claims 33-35 wherein said secondary substrate comprises an array of sensor units connected to primary substrates, wherein the wires are incorporated in the primary substrate material, said primary substrates being connected to said sensor units preferably in the form of pillars.

37. A sensor according to claim 36 wherein said sensor units are cantilevers and said primary substrates are in the form of pillars.

38. A sensor according to any one of the preceding claims wherein said sensor is in the form of a microchip.

39. A sensor according to any one of the preceding claims wherein said sensor further comprises a fluid channel, said sensor units protruding into said fluid channel.

40. A sensor according to claim 39 wherein said fluid channel includes an interaction chamber, said sensor units preferably being integrated into the wall of said interaction chamber.

41. A sensor according to any one of the preceding claims wherein said sensor comprises at least one sensor unit having a target surface area, which area has been

functionalised by linking, preferably by covalently linking of one or more functional groups comprising a detection ligand to said target surface area, said detection ligand being a member of a specific binding pair.

42. A sensor according to any one of the preceding claims wherein the sensor comprises at least two sensor units, at least one of said sensor units being a reference units.

43. A sensor according to claim 42 wherein said reference unit comprises a target surface area, which area has a surface chemistry different from the sensor unit for which the reference unit acts as reference, preferably said target surface area has been functionalised by linking, preferably by covalently linking of one or more functional groups, wherein said one or more functional groups linked to the surface area of said reference unit or its concentration are different from the sensor unit for which the reference unit acts as reference.

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Modtaget PVS

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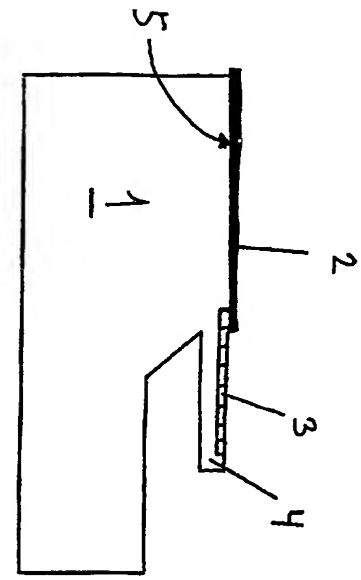


Fig 1

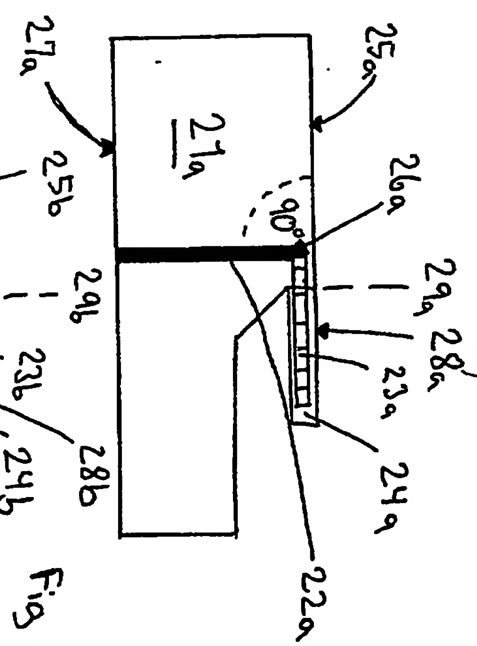


Fig 2a

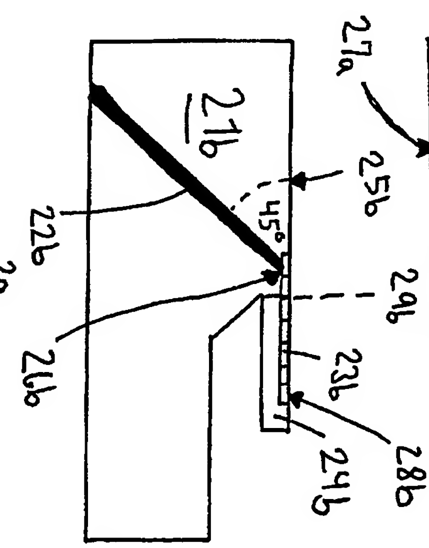


Fig 2b

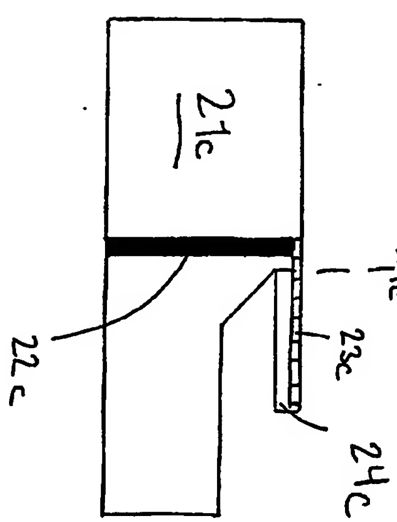


Fig 2c

Fig 3

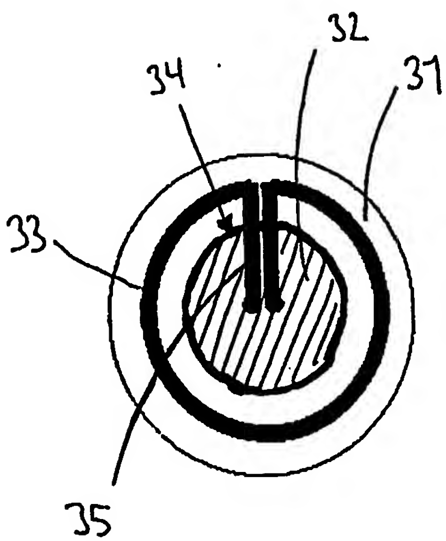


Fig 4

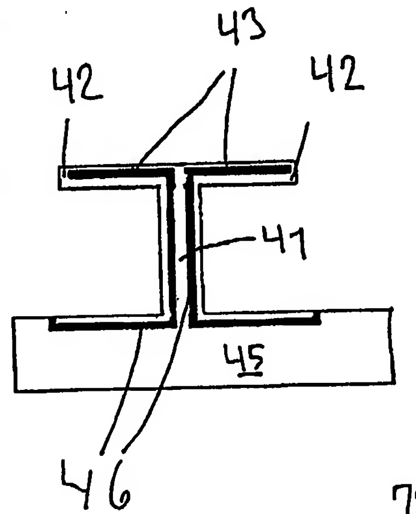


Fig 5

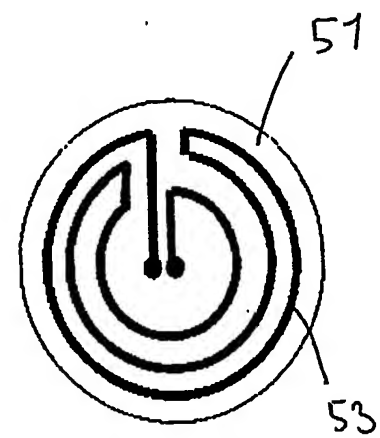
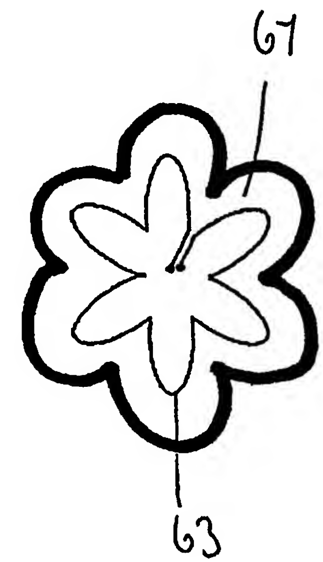


Fig 6



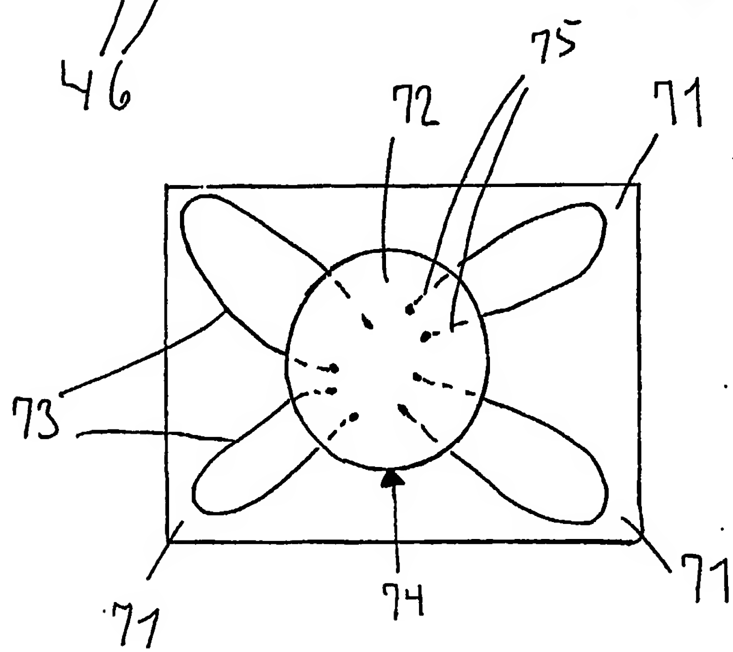


Fig 7

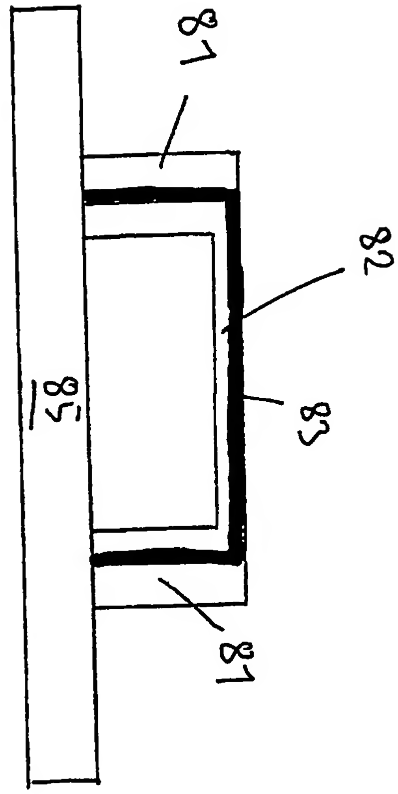


Fig 8

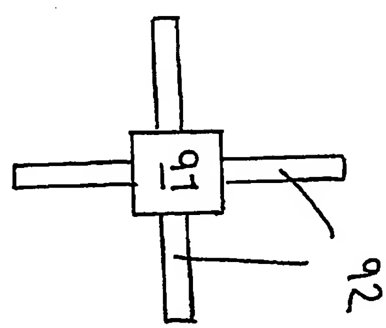


Fig 9